ELSEVIER

Clinical Outcome of Pancreas Transplantation From Marginal Donors in Japan

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ABSTRACT

In Japan, absolute shortage of donors still continues even after the law allowing organ transplantation from deceased donors came into force in 1997. With the passage of the waiting period after registration for pancreas transplantation (PTx), both deaths and serious cases of diabetic complications necessitating withdrawal of the registration have undoubtedly increased. Therefore, so-called "marginal donor" (MD) has been considered as a potential solution for shortage of donors in Japan. The aim of the present study is to evaluate feasibility of MD in terms of post-PTx outcomes using data from Japan Organ Transplantation Network. A total of 148 PTx were performed from deceased donors in Japan from 2000 to 2012. MD was defined as follows: (1) >45 years old; (2) hemodynamically unstable at harvest using a high-dose dopamine or more than 2 vasopressors; or (3) non–heart-beating status. Postoperative outcomes after PTx were compared between the MD group and the non-MD group. Among the 148 PTx donors, 108 donors (73.0%) satisfied the criteria of MD. Early graft loss of pancreas graft during 3 months post-transplant was observed in 15 patients (10.1%), and the marginality (MD vs non-MD) was not significantly correlated with the early loss of pancreas graft. The overall patient survival of the MD group (1, 3, 5 years: 94.7%, 94.7%, 94.7%) was not significantly different from that of the non-MD group (1, 3, 5 years: 95.0%, 95.0%, 95.0%). Pancreas graft survival in the MD group (1, 3, 5 years: 80.9%, 73.2%, 66.0%) seemed to be slightly lower than that in the non-MD group (1, 3, 5 years: 92.5%, 85.2%, 77.4%), but no statistically significant differences were found between the 2 groups. These results suggest the feasibility of the use of MD for PTx.

PANCREAS TRANSPLANTATION (PTx) is an established treatment for type 1 diabetes [1–3]. It is the only effective therapeutic option to restore normal glucose metabolism, to improve quality of life of the patients, and to even reduce chronic complications of the diabetes. Although its outcome was not satisfactory previously, graft survival has much improved during the last 30 years because of development in immunosuppressants, surgical techniques, and postoperative management.

In Japan, the Organ Transplant Law was enforced on October 1997, and it was revised on July 2010. Since the revision, the number of donation is increasing. However, absolute shortage of donors still continues even after the revision. With the passage of the waiting period after registration for PTx, both deaths and serious cases of diabetic complications necessitating withdrawal of the registration have undoubtedly increased. Accordingly, we have had to depend on the so-called "marginal donor" (MD). To date, however, the feasibility of PTx from MD has not yet investigated well. In this regard, the present study was performed to evaluate its feasibility in terms of postoperative outcomes using data from Japan Organ Transplantation Network.

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PATIENTS AND METHODS

Patients

Between April 2000 and December 2012, a total of 148 PTx were performed for type 1 diabetes from deceased donors in Japan. Among the 148 cases of PTx, 146 cases were from brain-dead donors and the remaining 2 were non–heart-beating donors. In Japan, PTx is performed in 17 approved institutions. Characteristics of the 148 patients are shown in Table 1.

Criteria of Marginal Donor

The criteria of MD for PTx of Kapur et al were used in this study; donors of 45 years of age and more, hemodynamically unstable donors at the time of harvest (with dopamine dose > 10 μg/k/min, or 2 or more vasopressors), or non–heart-beating donors [4]. Based on these criteria, the donors were divided into 2 groups: the MD group and the non-MD group.

Graft Failure

Pancreas graft failure was defined as return to insulin-dependence or serum C-peptide level < 0.3 ng/mL. Kidney graft failure was defined as return to dialysis. Death with a functioning graft was also considered be a graft failure. Early graft loss was defined as that within 3 months post-PTx in this study.

Statistical Analysis

Survival was calculated according to the Kaplan–Meier method and compared using the log-rank test. Statistical analysis was performed using StatView (version 5.0; SAS Institute Inc., Cary, NC, United States). A P value <.05 was considered statistically significant.

Table 1. Characteristics of 148 PTx Patients (n = 148)

Factors	
Donor-related factors	
Age (≤45 y/>45 y)	74/74
Gender (male/female)	80/68
Body mass index (kg/m^2) (<25/≥25)	115/33
Cause of death (CVA/trauma/others)	87/28/33
Type of death (brain-dead/non–heart-beating)	146/2
Hemodynamics (stable/unstable)	87/61
Cardiopulmonary resuscitation (−/+)	86/62
Marginality (MD/non-MD)	108/40
Recipient-related factors	
Age (≤50 y/>50 y)	123/25
Gender (male/female)	56/92
Duration of diabetes (<30 y/≥30 y)	90/58
Duration of dialysis (<10 y/≥10 y)	72/47
PTx-related factors	
TCIT (<12 h/≥12 h)	86/62
Type of PTx (SPK/PAK/PTA)	119/20/9
Duct management (bladder drainage/enteric drainage)	30/118
GDA reconstruction (−/+)	35/87
Immunosuppressive regimen	
CNI (TAC/CyA)	144/4
Antibody (−/+)	7/141

Abbreviations: PTx, pancreas transplantation; CVA, cerebrovascular accident; MD, marginal donor; TCIT, total cold ischemic time; SPK, simultaneous pancreas and kidney transplantation; PAK, pancreas transplantation after kidney transplantation; PTA, pancreas transplantation alone; GDA, gastroduodenal artery; CNI, calcineurin inhibitor; TAC, tacrolimus; CyA, cyclosporine.

RESULTS

Ratio of Marginal Donors

Among the 148 donors at the PTx, 74 were 45 or more years old. Sixty-one donors were hemodynamically unstable at the time of harvest. Two donors were non–heart-beating donors. In total, 108 donors (73.0%) of the 148 donors satisfied the criteria of MD and categorized into the MD group, and the remaining 40 donors (27.0%) were categorized into the non-MD group. Characteristics of the 148 patients are shown in Table 1.

Risk Factors for Early Loss of Pancreas Graft

Among the 148 PTx cases, early graft loss of pancreas graft was observed in 15 patients (10.1%). Thrombosis was the most frequent cause of the graft loss (8/15, 53%). The other causes were as follows: sepsis in 3, rejection in 2, duodenal perforation in 1, and cardiogenic shock in 1.

To investigate whether the marginality (MD vs non-MD) is a risk factor for the early loss of pancreas graft, as well as to identify factors that significantly correlate with the early graft loss, donor-related factors were compared between cases with the early graft loss and without the early graft loss (Table 2). The incidence of the early graft loss was significantly higher in donors with total cold ischemic time (TCIT) ≥12 hours (P = .05), and the marginality (MD vs non-MD) was not significantly correlated with the graft loss.

Long-Term Outcome After Pancreas Transplantation

We examined long-term outcomes of PTx in terms of overall patient survival, pancreas graft survival, and kidney graft survival (SPK cases). As shown in Table 3, in all the 148 cases, postoperative mortality was found in 5 patients in the MD group (4.6%) and in 3 patients in the non-MD group (7.5%). The incidence was not significantly different between the 2 groups (P = .45). Overall patient survival in the 148 cases was 94.8%, 94.8%, and 94.8% at 1, 3, and 5 years, respectively. The overall patient survival of the MD group (1, 3, 5 years: 94.7%, 94.7%, 94.7%) was not significantly different from those of the non-MD group (1, 3, 5 years: 95.0%, 95.0%, 95.0%; P = .42, Fig 1A). Twenty-four pancreas grafts were lost during the observation period

Table 2. Correlation of Donor-Related Factors With Early Loss of Pancreas Graft in the 148 PTx Cases

Factor	Early Graft Loss (−) (n = 133)	Early Graft Loss (+) (n = 15)	P Value
Age (≤45 y/<45 y)	66/67	8/7	.79
Gender (male/female)	70/63	10/5	.41
Body mass index (kg/m^2) (<25/≥25)	103/30	12/3	.56
Cause of death (CVA/others)	78/55	10/5	.59
Hemodynamics (stable/unstable)	80/53	7/8	.41
Cardiopulmonary resuscitation (−/+)	78/55	8/7	.78
TCIT (<12 h/≥12 h)	81/52	5/10	.05
Marginality (MD/non-MD)	96/37	12/3	.76

Abbreviations: PTx, pancreas transplantation; CVA, cerebrovascular accident; MD, marginal donor; TCIT, total cold ischemic time.

Table 3. Incidence of Mortality and Graft Failures in MD Group and Non-MD Group

	MD Group	Non-MD Group	*P* Value
Mortality	5/108 (4.6%)	3/40 (7.5%)	.45
Cardiogenic	1	2	
Cerebral bleeding	1	0	
Sepsis	2	1	
GVHD	1	0	
Pancreas graft failure	24/108 (22.2%)	4/40 (10.0%)	.08
Thrombosis	7	1	
Duodenal perforation/ bleeding	2	0	
Pancreatitis	1	0	
Recurrent diabetes	2	0	
Rejection	12	3	
Kidney graft failure	8/88 (9.1%)	1/31 (3.2%)	.44
Thrombosis	0	0	
Primary nonfunction	1	0	
Rejection	7	1	

Abbreviations: MD, marginal donor; GVHD, graft-versus-host disease.

among the 108 cases in the MD group, and 4 pancreas grafts were lost in the 40 cases in the non-MD group (Table 3). The incidence of the pancreas graft failure in the MD group tended to be higher than the non-MD group ($P = .08$, Table 3). Especially, thrombosis and rejection were frequently observed as a cause of the graft failure in the MD group. Pancreas graft survival in all the 148 cases was 84.8%, 76.4%, and 68.9% at 1, 3, and 5 years, respectively. Pancreas graft survival in the MD group and the non-MD group was 80.9% and 92.5%, 73.2% and 85.2%, and 66.0% and 77.4% at 1, 3, and 5 years post-PTx, respectively, and there was no significant difference between the 2 groups ($P = .35$, Fig 1B). Incidence of kidney graft failure in 119 SPK cases was also compared. The incidence was not significantly different between the 2 groups ($P = .44$, Table 3). Kidney graft survival in the SPK cases was 84.8%, 76.4%, and 68.9% at 1, 3, and 5 years, respectively. Kidney graft survival of the MD group (1, 3, 5 years: 89.1%, 89.1%, 86.0%) was not significantly different from that of the non-MD group (1, 3, 5 years: 93.5%, 93.5%, 84.2%; $P = .77$, Fig 1C).

DISCUSSION

The present study first showed that MD has been mostly utilized for PTx in Japan, compared with the condition of PTx donors in the United States [2,3]. However, the patient survival and graft survival were not significantly different from that in the United States. In case of simultaneous liver harvest in Japan, the reconstruction of gastroduodenal artery in pancreas graft has been done as much as possible (71.3%) to increase the blood flow in pancreas head region [5]. It remains unknown whether this procedure will have an effect on the early graft outcome.

The present study also demonstrated that there are no statistically significant differences in long-term outcomes after PTx between the MD group and the non-MD group. Furthermore, we investigated risk factors for the early loss of pancreatic graft and found that the marginality (MD vs non-MD) is not statistically significantly correlated with the early loss. These findings suggested the possibility that PTx from MDs is feasible in terms of postoperative outcomes. We also showed that the incidence of the early pancreatic graft loss within 3 months posttransplant is significantly increased when TCIT is over 12 hours. On the other hand, in the United States, it has been reported that preservation time of pancreatic graft >20 hours is significantly associated with post-PTx complications [6,7]. In this regard, a permissive range of the preservation time is likely to be narrow in Japan as compared to the United States where non-MDs are mostly available.

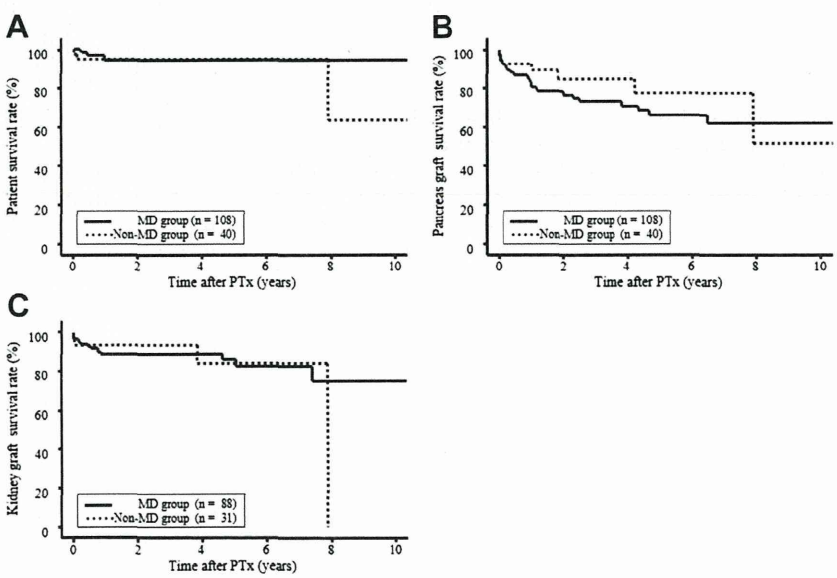

Fig 1. Long-term outcome after pancreas transplantation. Overall patient survival (**A**), pancreas graft survival (**B**), and kidney graft survival (**C**) were compared between the MD group (solid lines) and the non-MD group (dotted lines). Overall patient survival and pancreas graft survival were calculated in all the 148 PTx cases, and kidney graft survival was calculated in 119 simultaneous pancreas and kidney transplantation cases. Survival was not significantly different between the 2 groups. MD, marginal donor; PTx, pancreas transplantation.

In addition to the preservation time of the graft, to date, many donor-related risk factors have been considered as key determinants of outcomes after PTx such as donor age, obesity, donation after cardiac death, and cause of death. Especially, donor age is one of the most common risk factors. In general, aging affects nearly all the kinds of cells that play roles in outcomes of PTx including insulin-producing islet cells and endothelial cells of blood vessels, potentially affecting formation of thrombus. Salvalaggio et al reported from the United States data that old donors (>45 years) result in poorer long-term outcome in comparison to younger donors [8]. European data suggest equivalent outcomes [9]. Furthermore, donor age has been recognized as one of the factors composing scoring index for assessment of donor risk [10,11].

Indeed, the results of the present study may help expand the donor pool and resolve the donor shortage by using pancreas from MD. However, based on these previous reports, there seems to be another possibility that the current study enrolled too few cases to find statistically significant differences in post-PTx outcomes between the MD group and the non-MD group. Actually, the incidence of the pancreas graft failure in the MD group tended to be higher than the non-MD group, though the difference of the incidence was not statistically significant. To allow any conclusion on whether usage of grafts from MD is an acceptable option at PTx, studies with larger PTx numbers will be needed. If the outcome of PTx from MDs is judged to be worse than those from non-MDs, further investigations may be also necessary to clarify factors that contribute to better outcomes in MDs.

In summary, the current study suggested that PTx from MDs is feasible in terms of postoperative outcomes based on data obtained so far from a nationwide database in Japan. At the same time, considering the small number of PTx in Japan compared to other countries, the finding should be validated in studies with a larger number of PTx cases.

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Question 72
C型肝炎ウイルスとスタチン・肝細胞癌との関連について

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Answer

近年，C型肝炎に対する新たな治療薬として，プロテアーゼ阻害剤やポリメラーゼ阻害剤の開発が飛躍的に進んでおり，わが国でも，これまでの標準的な治療法であるPEGインターフェロン（PEG-IFN）とリバビリン（RBV）併用療法にプロテアーゼ阻害剤を加えた3剤治療が認可され，難治性のGenotype 1b型の患者に対しても，ウイルス学的著効（sustained virological response：SVR）率が70％にまで向上しつつある。しかし，副作用や高齢者，耐性ウイルスの出現などの問題もあり，今後もPEG-IFN/RBV併用療法が主要な治療のひとつであり，その効果を改善させるためのさまざまな工夫がなされてきた。

その工夫のひとつとして，高脂血症治療薬のHMG-CoA還元酵素阻害剤であるスタチン製剤の併用が挙げられる。Yeらは，*in vitro*においてスタチン製剤のひとつであるlovastatin（国内未承認）がC型肝炎ウイルス（hepatitis C virus：HCV）のRNA複製を抑制することを初めて報告した[1]。わが国でもIkedaらが，HCV RNA複製クローン細胞を用いて国内で承認されている5種類のスタチン製剤（アトルバスタチン，シンバスタチン，プラバスタチン，フルバスタチン，ピタバスタチン）の抗HCV効果について検討し，プラバスタチンを除く4種類のスタチン製剤でローバスタチンよりも強いHCV増殖抑制効果を示し，さら

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に IFN-α との併用により相乗的な抗 HCV 効果を認めたことを報告している[2]。

スタチン製剤による HCV 増殖抑制の作用機序として，コレステロールはアセチル-CoA から HMG-CoA，メバロン酸，ゲラニルピロリン酸，ファーネシルピロリン酸などの中間産物を経て生合成される（図 1）。このうち，ゲラニルゲラニルピロリン酸は，転写酵素により宿主蛋白質に結合（ゲラニルゲラニル化）し生理活性を調整する作用をもち，そのゲラニルゲラニル化される宿主蛋白質の一部が HCV RNA の複製に必要である。スタチン製剤は HMG-CoA からメバロン酸の合成を行う HMG-CoA 還元酵素を抑制することでコレステロールの生合成を抑制することが知られているが，中間産物であるゲラニルゲラニルピロリン酸生合成も抑制するため HCV RNA の複製が抑制されるとされている[1]。

臨床においても，Sezaki らが Genotype1b 型，高ウイルス量の C 型慢性肝炎患者 21 例に対し，PEG-IFN/RBV 療法にフルバスタチンを併用投与し，コントロール群に比して HCV RNA の陰性化率が有意に高いことを報告している（図 2）[3][4]。

一方，スタチン製剤には肝発癌を抑制する可能性も指摘されている。Tsan らは，C 型慢性肝炎患者の肝癌発症とスタチン製剤の関連性を評価するために C 型慢性肝炎患者 260,864 人を対象としたコホート研究を行い，スタチン非投与群に比してスタチン製剤投与群において肝癌の発症率が 47％

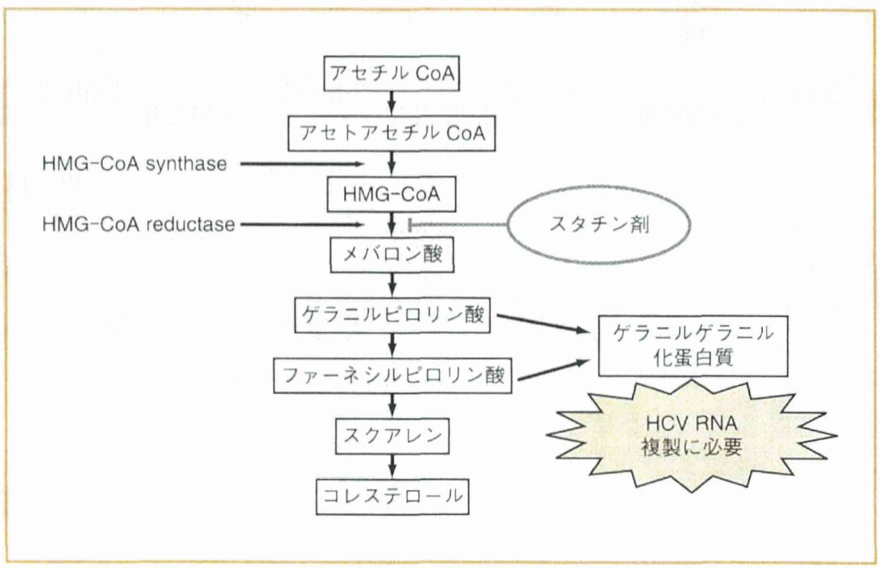

図 1　コレステロール生合成とスタチン剤

（文献 1 より改変引用）

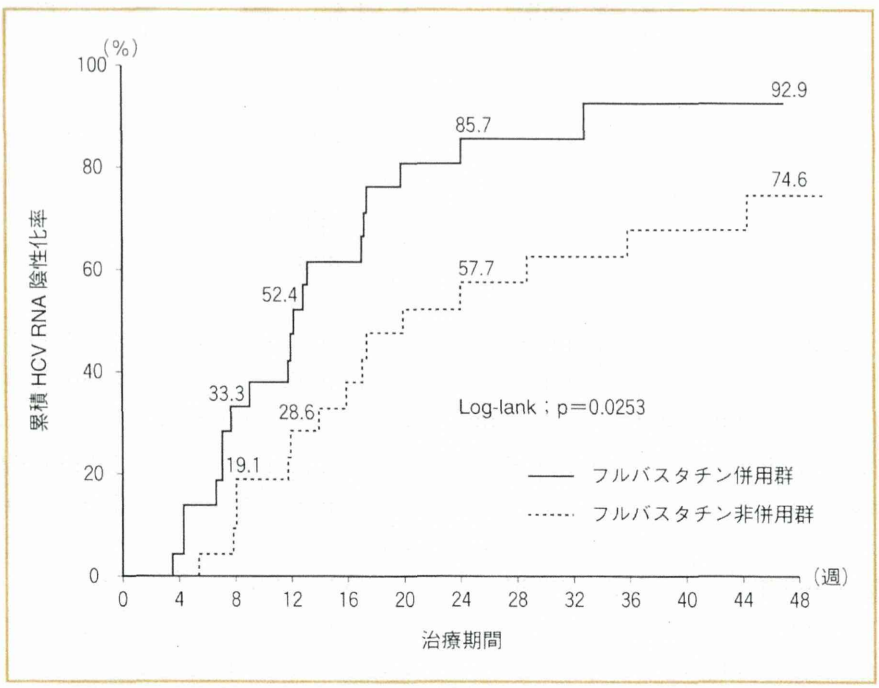

図 2　フルバスタチン併用群と非併用群における HCV RNA 陰性化率の推移

（文献 3 より改変引用）

低下することを報告している[5]。

肝癌発症のリスク軽減に関するスタチン製剤の作用機序については，コレステロール合成やHCV RNA複製の抑制によりHCVの活性を抑制すること以外に，ゲラニルゲラニルピロリン酸などの代謝産物の生合成を抑制することで腫瘍細胞に対してアポトーシスや細胞周期の停止を誘導すること[6]などが報告されている。

スタチン製剤は，HCVの増殖や複製を抑制することでPEG-IFNとRBVの2剤併用治療の効果を向上し，さらに肝発癌を抑制する可能性のある薬剤である。特に，プロテアーゼ阻害剤による3剤治療が適応とならない慢性C型肝炎症例に対しては，スタチン製剤を併用することで治療効果の向上が期待される。

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RETROSPECTIVE STUDY

Clinicopathological features of small nonfunctioning pancreatic neuroendocrine tumors

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Abstract

AIM: To present our experiences in studying the clinicopathological features of small nonfunctioning pancreatic neuroendocrine tumors (NF-pNETs).

METHODS: The subjects included 9 patients with NF-pNETs who underwent pancreatectomy between April 1996 and September 2012. The surgical procedure, histopathological findings, and prognosis were assessed.

RESULTS: All tumors were incidentally detected by computed tomography. The median diameter was 10 mm (5-32 mm). One patient was diagnosed with von Hippel-Lindau disease, and the others were sporadic cases. For the histopathological findings, 7 patients were G1; 1 patient was G2; and 1 patient, whose tumor was 22 mm, had neuroendocrine carcinoma (NEC). One patient who had a tumor that was 32 mm had direct invasion to a regional lymph node and 1 patient with NEC, had regional lymph node metastases. Six of the 7 patients with sporadic NF-pNETs, excluding the patient with NEC, had tumors that were smaller than 10 mm. Tumors smaller than 10 mm showed no malignancy and lacked lymph node metastasis.

CONCLUSION: Sporadic NF-pNETs smaller than 10 mm tend to have less malignant potential. These findings suggest that lymphadenectomy may be omitted for small NF-pNETs after further investigation.

Key words: Pancreatic neuroendocrine tumor; Pancreatic neuroendocrine carcinoma; Nonfunctioning; Lymphadenectomy; Treatment

Core tip: We present our experience in studying the clinicopathological features of small nonfunctioning pancreatic neuroendocrine tumors (NE-pNETs). In the present study, six of the 7 patients with sporadic NF-pNETs, excluding the patient with NEC, had small tumors that were less than 10 mm. These small tumors showed no sign of malignancy or lymph node metastasis. Additionally, these cases did not have recurrence, including lymph node and distant metastasis, for more than 10 years after surgery. These findings suggest that small NF-pNETs tend to have less malignant potential and no lymph nodes metastasis. Lymphadenectomy may be omitted in the future for small NF-pNETs after further investigation.

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INTRODUCTION

Pancreatic neuroendocrine tumors (pNETs) are relatively rare, accounting for 1%-2% of all pancreatic neoplasms[1]. Although pNETs progress slowly and have better a prognosis than pancreatic cancer, pNETs have malignant potential, including features of local invasion, lymph node metastasis, and distant metastasis. The appropriate diagnosis and treatment of pNETs are crucial. These tumors are classified into functioning pNETs (F-pNETs), which present with specific symptoms due to excess hormones, and nonfunctioning pNETs (NF-pNETs), which do not present with these symptoms. Because NF-pNETs do not present with specific symptoms, they are often detected as large tumors in the advanced stage, with distant metastasis or invasion to adjacent organs. However, improvements in diagnostic imaging over the last few decades have led to the incidental detection of small NF-pNETs *via* diagnostic imaging for the work-up of other conditions. The incidence of malignancy reportedly increases with larger NF-pNETs[2,3]. However, even small NF-pNETs have malignant potential and may spread to lymph nodes or metastasize to distant sites. Therefore, once NF-pNETs are diagnosed, all cases are considered for surgical resection[4]. The significance of lymph node metastasis in the NF-pNETs has been reported[5-9]; the prognosis is poor with a 5-year survival of 49.4%, even after resection, in cases with lymph node metastasis[7]. Therefore, lymphadenectomy, in addition to tumor resection, is recommended when the tumor is malignant or when lymph node metastasis is suspected. However, there are no standard criteria for lymphadenectomy when small, asymptomatic, and incidentally detected NF-pNETs are identified. The inclusion of lymphadenectomy during surgery for NF-pNETs remains controversial.

In the present study, we report 9 cases of NE-pNETs treated at our hospital over the last 16 years.

MATERIALS AND METHODS

Between 1996 and 2012, 26 patients with pNETs underwent pancreatectomy at Asahikawa Medical University Hospital, of whom 9 patients were diagnosed with NF-pNETs and were further investigated. The diagnosis of pNET was established by histopathological examination and immunohistochemical staining of surgical specimens with chromogranin A, synaptophysin, and neuron-specific enolase stain. Tumors were classified as nonfunctioning regardless of the plasma hormone levels or immune activity of the tissue if the patient lacked the clinical symptoms that are typically caused by excess hormones. The patients' medical records were retrospectively reviewed. All patients were pathologically classified according to the criteria established by the WHO 2010 classification of endocrine tumors[4]. An immunohistochemical staining assay for Ki67 was performed for all patients. The Ki67 proliferative index is expressed as a percentage based on the count of Ki67-positive cells in a set of 2000 tumor cells in areas with the highest immunostaining, which was evaluated with the MIBI antibody, and the cases were classified into the following 3 categories: G1 (mitoses/10 HPFs < 2 and/or Ki67 index < 3), G2 ($2 \leqslant$ mitoses/10 HPFs $\leqslant 20$ and/or $3 \leqslant$ Ki67 index $\leqslant 20$), and neuroendocrine carcinoma (NEC) (mitoses/10 HPFs > 20 and/or Ki67 index > 20). The tumor size was defined by the largest diameter of the tumor. A TNM stage group was assigned to each case based on the European Neuroendocrine Tumor Society (ENETS) staging classification for pNETs[10]. The postoperative follow-up included clinical examination, the blood neuron specific γ-enolase (NSE) level, and contrast-enhanced computed tomography (CT) scanning. CT scans were performed every 6 to 12 mo in the first year, then annually thereafter.

RESULTS

In this study, the tumors identified as NF-pNETs accounted for 2.8% of all pancreatic neoplasms (9/220) and for 35% of pNETs (9/26). Table 1 summarizes the clinical features, surgical procedure, histopathological findings, prognosis, WHO classification, and ENETS TNM classification of the 9 patients diagnosed with NF-pNETs. These patients included 3 men and 6 women with a mean age of 67 years (range, 47-75 years) at the time of surgery. One patient with von Hippel-Lindau disease had previously undergone enucleation of the pNETs; the others were sporadic cases. All patients with NF-pNETs were asymptomatic, and none had evidence of distant metastasis. In all cases, the pancreatic tumors were incidentally detected by radiological investigation during evaluations for unrelated conditions. None of the patients had a preoperatively elevated blood level of NSE. Three patients underwent endoscopic ultrasonography-fine needle aspiration (EUS-FNA) and were preoperatively diagnosed with pNETs (No. 2, 6, and 8). All patients underwent surgical resection of the pancreas: 3 patients underwent distal pancreatectomy (DP), 2 patients underwent pylorus-preserving pancreatoduodenectomy (PPPD), 2 patients underwent subtotal stomach-preserving pancreatoduodenectomy (SSPPD), and 2 patients underwent partial resection of the pancreas. R0 resection was performed in all patients, except in 1 patient who underwent partial resection with positive surgical margins (No. 5). Regional lymphadenectomy was performed in 5 of the 9 patients (No. 2, 3, 6, 7, and 8). The median tumor diameter was 10 mm (range, 5-32 mm). All patients, except for the patient with von Hippel-Lindau disease (4 tumors), had a single tumor. Six patients had tumors located in the head

Table 1 Clinical and pathological status of 9 patients with nonfunctioning pancreatic neuroendcrine tumors

No	Age (yr)	Sex	Size (mm)	Location	Number of tumor	EUS-FNA	Preoperative diagnosis	Surgical procedure	Lymphadenectomy	Metastases		Motoses	Ki67/ MiB-1 (%)	WHO classification 2010	TNM classification (ENET)	Prognosis (mo)
										Lymph node	Distant					
1	58	F	32	Ph	1	No	Pancreatic tumor	DP	No	Direct Invasion	No	0	0.2	NET G1	T2N1M0	59 alive
2	73	M	22	Ph	1	No	NET	PPPD	Regional	No	No	1	5.8	NET G2	T2NOMO	39 alive
3	67	F	22	Pb	1	Done	NET G1	DP	Regional	Positive	No	20	20	NEC	T2N1M0	14 alive
4	74	F	10	Pb	1	No	Islet cell tumor	DP	No	No	No	0	1.6	NET G1	T1N0M0	196 alive
5	61	M	10	Pb	1	No	Islet cell tumor	Partial resection	No	No	No	0	0.1	NET G1	T1N0M0	135 alive
6	51	F	9	Ph	1	Done	NET G1	PPPD	Regional	No	No	0	1	NET G1	T1N0M0	64 alive
7	47	F	6	Ph	4	No	NET	SSPPD	Regional	No	No	0	0.9	NET G1	T1N0M0	22 alive
			2.1												Stage I	
			1.2													
			1.2													
8	75	M	6	Ph	1	Done	NET G1	SSPPD	Regional	No	No	0	< 1	NET G1	T1N0M0	20 alive
9	56	F	5	Ph	1	No	Cartinoid	Partial resection	No	No	No	0	0.4	NET G1	T1N0M0	34 alive

EUS-FNA: Endoscopic ultrasonography-fine needle aspiration; Ph: Head of pancreas; Pb: Body of pancreas; DP: Distal pancreatectomy; PPPD: Pylorus-preserving pancreatoduodenectomy; SSPPD: Subtotal stomach preserving pancreatoduodenectomy.

of the pancreas, while 3 patients had tumors located in the body of the pancreas. Seven patients were classified as G1, and 1 patient with a tumor that was 22 mm in diameter was classified as G2. Although 1 patient, with a tumor that was 22 mm in diameter, was diagnosed as G1 by preoperative EUS-FNA, the final diagnosis was neuroendocrine carcinoma (NEC). None of the patients, except two cases, had no lymph nodes metastasis; one with lymph node metastasis had a tumor that was 32 mm in diameter with direct invasion to the regional lymph nodes, and the other had NEC with regional lymph nodes metastasis. Six of the 7 patients with sporadic NF-pNETs had small tumors that were less than 10 mm in size; one patient with NEC had a larger tumor. Tumors that were less than 10 mm in size showed no malignancy, were well differentiated, and lacked lymph node metastasis. Six patients were classified as Stage Ⅰ, 1 patient was classified as Stage Ⅱa, and 2 patients were classified as Stage Ⅲb. With respect to the postoperative complications, three patients had a pancreatic fistula, one patient was classified as Grade B (No. 3), and 2 patients were classified as Grade A (No. 1 and 2) according to the ISGPS criteria. None of the patients in this study had exocrine or endocrine insufficiency. The mean follow-up period was 63 mo (range, 14-196 mo). All of the patients are currently alive without disease recurrence according to radiological imaging.

DISCUSSION

In the present study, we examined the NF-pNETs in 9 patients who underwent pancreatectomy at our institution over the last 16 years. For all of the patients, the tumors were incidentally detected by diagnostic imaging during a work-up for other conditions. Most tumors were small, with a diameter of 5-32 mm (median: 10 mm), and none of the tumors showed evidence of distant metastasis. While the larger tumors tended to be associated with direct invasion of the lymph nodes and lymph node metastases, a high Ki-67 index, and an advanced TNM stage, tumors that were smaller than 10 mm in diameter lacked malignancy and lymph node metastasis.

NF-pNETs are relatively rare, and only 9 patients presented with NF-pNETs at our institution over the last 16 years. In Western nations, pNETs occur at an incidence of 1 per 100000 individuals and represent 1%-2% of all pancreatic neoplasms[1]. Over the last few years, however, this incidence has increased[11,12]. An epidemiological study by NETWork Japan in 2005 estimated that the incidence of pNETs per 100000 individuals is 2.23 patients in Japan. Compared with Western nations, Japan has a 2- to 3-fold higher incidence of pNETs[3]. In total, 30%-50% of all pNETs are nonfunctioning[3,13]; however, because NF-pNETs do not present with characteristic clinical symptoms due